

Table 4. Multivariate analyses of grade 2 to 4/grade 3 to 4 acute graft-versus-host disease, and chronic/extensive-type chronic graft-versus-host disease.

Outcome	Grade 2 to 4 acute GVHD				Grade 3 to 4 acute GVHD				N.	Chronic GVHD			Extensive-type chronic GVHD		
	N.	RR	95%CI	P	RR	95%CI	P	RR		95%CI	P	RR	95%CI	P	
Children 15 years or younger															
HLA disparity															
Matched (6/6)	72	1.00			1.00			67	1.00			1.00			
5/6	196	2.13	(1.28-3.58)	0.004	1.75	(0.73-4.24)	0.212	186	1.79	(0.85-3.75)	0.123	4.15	(0.54-31.81)	0.17	
4/6	136	2.65	(1.55-4.52)	<0.001	2.25	(0.94-5.41)	0.07	114	2.99	(1.42-6.30)	0.004	7.62	(1.03-56.63)	0.047	
3/6	28	2.39	(1.18-4.84)	0.015	2.60	(0.82-8.26)	0.105	23	2.61	(0.96-7.11)	0.061	7.49	(0.81-69.63)	0.077	
Adults 16 years or older															
HLA disparity															
Matched (6/6)	56	1.00			1.00			49	1.00			1.00			
5/6	227	1.03	(0.64-1.65)	0.916	0.95	(0.38-2.37)	0.919	193	1.58	(0.83-3.02)	0.161	1.15	(0.47-2.80)	0.758	
4/6	765	1.27	(0.82-1.97)	0.276	1.27	(0.55-2.94)	0.573	650	1.90	(1.03-3.51)	0.04	1.62	(0.71-3.72)	0.253	
3/6	341	1.72	(1.10-2.70)	0.017	1.13	(0.47-2.68)	0.788	288	1.81	(0.96-3.38)	0.065	1.28	(0.54-3.02)	0.574	

For grade 2 to 4 acute GVHD, other predictive variables were total nucleated cell dose ($>10 \times 10^7/\text{kg}$ as the reference, $RR=1.94$ $P=0.009$ for $5.0-9.9 \times 10^7/\text{kg}$, $RR=1.73$ $P=0.028$ for $2.5-4.9 \times 10^7/\text{kg}$, and $R=1.68$ $P=0.094$ for $<2.5 \times 10^7/\text{kg}$) in children, and cyclosporine-based GVHD prophylaxis (vs. tacrolimus-based) in adults. For grade 3 to 4 acute GVHD, male sex and advanced disease status in children, and male sex and male to female donor-recipient sex mismatch and reduced-intensity conditioning in adults. For chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch, and male to female sex mismatch and advanced risk disease status for decreased risk. For extensive-type chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch.

number of adult recipients. Our findings in children were similar to those in previous reports.^{9,17,18,31,32} An increase in the number of HLA mismatches resulted in an increased risk of acute and chronic GVHD, which led to an increased risk of overall and transplant-related mortality. In contrast to the results in children, the probability of overall or relapse-free survival did not decrease with the number of mismatched antigens in adults. An increase in the number of HLA mismatches in UCB increased the incidence of cGVHD in 4/6 CB recipients; however, there was no increase in the risk of grade 2 to 4 or severe acute GVHD, or extensive-type chronic GVHD. These differences may have contributed to the decreased incidence of relapse without affecting TRM after HLA-mismatched UCBT in adults.

A major potential contributor to the different findings in children and adults is the difference in the nucleated cell dose. There was a dramatic difference in the nucleated cell dose between children and adults. TNC dose in adults is highly concentrated in a very small, low-dose area that is quite different from the doses used in children in our study and from the doses in previous reports, mainly in pediatric recipients.^{9,18,32} A positive effect on the transplant outcome with a decreased incidence of acute GVHD and lower mortality with HLA matching might only be seen in the setting of pediatric recipients who receive cord blood with a larger cell dose compared to adults. A report from Eurocord of 171 adult recipients of single-unit CBT did not see a decrease in the probability of overall or relapse-free survival with the number of mismatched antigens.³³ A more recent collaborative study by the Center for International Blood and Marrow Transplant Research, the New York Blood Center National Cord Blood Program, and the Eurocord-Netcord registry with 514 adult recipients did not observe an increase in mortality after HLA-mismatched UCBT.³⁴

Another potential cause of different findings in children and adults is differences in diagnosis. Adult recipients had a significantly greater proportion of patients with myeloid malignancy. The incidence of a graft-versus-leukemia effect is reportedly higher in myeloid malignancy.³⁵⁻³⁷ The decreased risk of relapse with a significant graft-versus-

leukemia effect in HLA-mismatched UCB recipients was also more prominent in adult recipients with acute myeloid leukemia in our study. Furthermore, there were differences in disease risk between children and adults. Only 36% of adults were in a standard-risk disease status at transplant, while this value was 50% in children. Although we had adjusted for the disease status at transplant, we cannot rule out the possibility that these differences influenced the results.

An increase in the total nucleated cell dose increased the neutrophil recovery rate in both children and adults, consistent with other reports.^{18,31-33} A lower total nucleated cell dose was not associated with increased transplant-related or overall mortality in our cohort, thus, we did not see a combined effect of HLA disparity and total nucleated cell dose. This differs from the findings of a recent report from New York Cord Blood Bank.¹⁸ In our cohort, a lower cell dose was associated with a slower recovery; however, the differences in the overall incidences of neutrophil recovery between cell dose groups were small, especially in the adult cohort. This may explain our finding that a lower total nucleated cell dose was not associated with increased mortality. Another probable reason for the different findings is that for our analyses we separated children and adults. A small percentage of older adults who received lower cell dose CB included in the subjects of previous studies may have affected increased mortality with lower cell doses. Lastly, TNC dose in adults is highly concentrated in a very small, low-dose area (nearly 70% lie in the range of $2.0-3.0 \times 10^7/\text{kg}$) which is a unique finding for adult recipients of single-unit cord blood in Japan. Therefore, differences in cell doses between the TNC dose groups is quite small, which is suspected to be one of the reasons for these findings. The results of our study support the current recommended cut-off TNC dose for cord blood search in Japan, which is $2.0 \times 10^7/\text{kg}$.

Although information is still limited because of the limited number of 6/6 and 5/6 CB adult recipients, the large number of adult recipients of 4/6 CB enabled us to analyze the association of outcomes with the type of HLA mismatches in this population. There was no effect of HLA mismatch type on overall mortality; therefore, there is no

preference recommendation for HLA mismatch types from our study. The increase in the number of HLA-DRB1 mismatch was associated with decreased mortality; however, it is important to note that HLA-DRB1 double mismatch was associated with increased transplant-related mortality.

This study included a large number of HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution typed CB recipients, but there are limitations. UCB selection is mainly influenced by the availability of an acceptable cell dose, but is also influenced by many unmeasured factors that can affect the outcome. Although we adjusted for known risk factors and disparities between groups, we cannot rule out the influence of a potential selection bias. Another limitation involves the results for 3/6. Since, in current practice in Japan, HLA-DR typing for UCB unit selection is performed at low resolution, with a preference of up to two HLA antigen-mismatched UCB units, most (97%) of the HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution 3/6 UCB in the present study were selected as one- or two-antigen-mismatched for the HLA-A, HLA-B, and HLA-DR low-resolution level. If we consider the effect of the current practice for UCB unit selection regarding 3/6 UCB, our conclusions should only apply to HLA-A, HLA-B, and HLA-DRB1 or HLA-A, HLA-B, and HLA-DR zero- to two-mismatched UCBT. Furthermore, we may have underestimated the impact of HLA-matching, since we did not have enough data to include low- or high-resolution information on HLA-C matching, which

was recently reported to affect mortality.³⁸

In conclusion, we found that the effects of HLA disparity on transplant outcome differed between children and adults. In children, an increased number of mismatched HLA loci correlated with an increased risk of mortality. These findings support the selection of a UCB unit with HLA 6/6 followed by 5/6, consistent with the recommendations from the US and Europe. In adults, there was no increase in mortality with an increase in the number of mismatched HLA loci. In this case, a UCB unit with up to 4/6 can be selected if transplant is urgently needed.

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